

### **REMARKS**

Applicant respectfully requests reconsideration of the present application in view of the foregoing amendments and in view of the reasons that follow.

#### **I. Status of the claims**

The amendments to claims 25 and 26 are the sole changes in the status of the claims.

The foregoing amendments add no new matter and are made solely to advance prosecution, without waiver or disclaimer of any subject matter. Following entry of the foregoing amendments, claims 14, 16-23, 25, 26, 40 and 41 are pending, of which claims 14, 25, 26, 40 and 41 are independent.

#### **II. Rejections under 35 U.S.C. § 112, second paragraph are overcome**

The amendments to claims 25 and 26 are believed to overcome their rejection under 35 U.S.C. § 112, second paragraph, as listed on page 2 of the Office Action. Reconsideration and withdrawal of the rejection are respectfully petitioned.

#### **III. Rejections under 35 U.S.C. § 112, first paragraph, enablement**

##### **A. The rejection**

The Examiner notes that the specification describes administration of antibodies against the IL-6 receptor at the same time, or shortly before, administration of cerulein to rodents. In the mind of the Examiner, the specification is enabled only for *prevention of disease in rodents*. Page 5 of the Office Action states that:

The issue at hand is a) whether treatment before the condition develops is predictive of treatment after acute pancreatitis occurs, and b) whether treatment by inhibition of IL-6 would be expected to be effective after acute pancreatitis has developed. None of the exhibits to which applicants refer show either treatment after development of acute pancreatitis, nor treatment of acute pancreatitis with any IL-6 inhibitor. Thus it remains that the sole working examples in the specification, which inhibit IL-6 prior to the induction of acute pancreatitis, are not

enabling of the claims, which are drawn to the treatment of (existing) acute pancreatitis.

The rejection therefore has several subsidiary aspects, each of which Applicant respectfully traverses the rejection because each is based on the incorrect legal standard and/or a misunderstanding of the facts. These are addressed individually, below.

**B. Enablement of treatment of humans based on animal models**

The assertion that the evidence of treatment in rats cannot be translated to human therapy is legally deficient in two aspects. The **first** is the apparent assumption that the art is too unpredictable to translate animal models to human therapy. As to this point, Applicant notes that:

There is no requirement for clinical data to prove that an application is in compliance with 35 U.S.C. § 112, first paragraph. In fact, description of *in vitro* and/or animal testing has been held to enable claims to *in vivo* therapeutic compositions and methods of their use.

*Cross v. Iizuka*, 753 F.2d 1040, 1050 (Fed. Cir. 1985); *see also In re Brana*, 51 F.3d 1560, 1567-68 (Fed. Cir. 1995) (holding that animal testing results are sufficient to establish whether one skilled in the art would believe that a pharmaceutical compound has an asserted clinical utility for the purposes of compliance with the enablement requirement of 35 U.S.C. § 112, first paragraph). Applying the relevant legal standards, therefore, Appellant is not required to show clinical effectiveness, but only such results that would be believed to support clinical utility.

The **second** (related to the first) is that the enablement requirement is keyed to the *perspective of one skilled in the art* (35 U.S.C. § 112, first paragraph; *see also*, e.g., MPEP 2164). The Examiner does not apply the perspective of the person of ordinary skill.

Exhibits G-K documented studies of pancreatitis in rodents. The Examiner considers that these are irrelevant. For example, “Exhibit G merely gives a list of references, and does not serve to show any information as to the issue at hand, which is whether of not

pretreatment with an IL-6 inhibitor would treat existing acute pancreatitis.” The Examiner ignores the purpose for which Exhibit G was cited, which is to show that there were 1248 PubMed references which demonstrate that *cerulein-induced pancreatitis is a very widely used model*. This point was specifically made in the response filed February 23, 2010. Indeed, Exhibits G-K were all cited as evidence for the widespread use of cerulein or other rodent models of pancreatitis. More importantly, Exhibit G-K demonstrate that cerulein and other rodent models are *considered to be appropriate models for human disease*.

Therefore, when the Examiner asserts that rodent models are not predictive of human therapy, the Examiner’s conclusion contradicts the perspective of those skilled in the art, and therefore applies the incorrect standard for assessing enablement. Applying the perspective of the person of ordinary skill, as required, the presently-used rodent model would be considered relevant to demonstrate enablement of therapy in human patients.

**C. Enablement of treatment when the agent is administered prior to the onset of pancreatitis.**

A separate issue is whether the person of ordinary skill would consider that the demonstration of prophylactic efficacy can be extrapolated to treatment of a pre-existing condition. Here, the questions concern both facts and law.

The Examiner states on page 5 of the Office Action that “[n]one of the exhibits to which applicants refer show either treatment after development of acute pancreatitis.” To the Examiner, this demonstrates the folly of relying on a rodent model of cerulein-induced pancreatitis to demonstrate treatment of pre-existing disease. However, the Examiner is making a *legal* error by substituting her perspective for the perspective of the person of ordinary skill.

Because the person of ordinary skill studies the *therapeutic* efficacy of an agent in a model in which the agent is administered before cerulein, Applicant has done no more or less than the person of ordinary skill in the art and is likewise entitled to infer therapeutic efficacy from the experimental results. Thus, the Examiner’s statement regarding the methodology

used in the references *support* the enablement of Applicant's claims because it shows that Applicant's method and conclusions comport with those of *the person of ordinary skill*.

For example, in Exhibit I (Michalski *et al. Gastroenterology* 132:1968-1978, 2007), cannabinoids were administered before, and during, induction of pancreatitis with cerulein. The authors conclude that their "results suggest a therapeutic potential for cannabinoids in abolishing pain associated with acute pancreatitis and in partially reducing inflammation and disease pathology in the absence of adverse side effects." *See, id.*, Abstract. So, to these researchers, the order of administration did not prevent a conclusion that the same drugs could be used for the treatment of pre-existing pancreatitis in humans.

Accordingly, by dismissing the perspective of the person of ordinary skill, this aspect of the rejection is based on a legal error. Concerning the *factual* error, mentioned above, the Examiner overlooks the dynamic reality of pancreatitis.

Inflammation-related diseases are characterized not only by a single initiating event, but continuous inflammation reactions such that inflammatory disease is typically not caused by only one inflammation reaction. To reproduce the actual disease conditions, therefore, cerulein must be administered repeatedly, as was done by Applicant and in the literature. Accordingly, any therapeutic agent must act not only to inhibit inflammatory reactions which have already occurred, but also to inhibit inflammatory reactions that may be caused after the administration of the agent.

Accordingly, administration of the antibody prior to a complete inflammatory reaction is relevant to demonstrating therapeutic efficacy of natural disease, because it models the efficacy of inhibiting on-going inflammatory events. There is no logical or factual discrepancy between prior administration of the antibody and the assertion of therapeutic efficacy of extant disease. Thus, one can conclude therapeutic efficacy from the present examples, because they show that when an antibody is administered prior to the inflammatory reaction caused by cerulein it clearly inhibited the inflammatory reaction caused by cerulein, and the weight gain of the pancreas was inhibited.

Applicant respectfully requests reconsideration and withdrawal of this aspect of the rejection.

**D. Treatment of acute pancreatitis enables treatment of the genus of pancreatitis**

While page 3 criticizes the breadth of the claims for encompassing “pancreatic edema due to *any* cause, and not merely acute pancreatitis” the Examiner has not explained why the person of ordinary skill would not consider that the evidence of record would not support the broader genus. If the inflammatory process mentioned above is common to all pancreatic edema, then it should be amenable to treatment by the same means. Reconsideration and withdrawal of this aspect of the rejection is requested.

**E. Treatment by an antibody against IL-6 receptor enables the full scope of all IL-6 inhibitors**

Here, it is not clear on which basis the Examiner rejects the scope of the claims, especially since the claims require an antibody that blocks signal transduction. Accordingly, the claims are limited to a specific genus of antibodies with a specific target protein, and a specific mechanism of action (from which also may be inferred a narrower set of epitopes). Reconsideration and withdrawal of this aspect of the rejection is requested.

**F. Summary**

The present rejection relies on errors of fact and law, most notably in failing to apply the perspective of the person of ordinary skill. Accordingly, Applicant believes that each aspect of the rejection, and the rejection as a whole, is in error and requests its withdrawal.

**CONCLUSION**

Applicant believes that the present application is now in condition for allowance. Favorable reconsideration of the application as amended is respectfully requested.

The Examiner is invited to contact the undersigned by telephone if it is felt that a telephone interview would advance the prosecution of the present application.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by the credit card payment instructions in EFS-Web being incorrect or absent, resulting in a rejected or incorrect credit card transaction, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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